idence for the oligomerization of thrombin and GpIbα in solution, and propose that thrombin could promote intramembranous clustering of GpIbα signaling complexes. In support of their model, catalytically inactive thrombin reportedly can signal through GpIb-IX-V after first cleaving GpV (*14*). On the other hand, Dumas *et al*. look at their structure and visualize thrombin as an adhesive ligand for GpIbα molecules on two membranes, zippering platelets together and promoting thrombus growth. However, mouse platelets lacking PAR4 do not aggregate upon treatment with 500 nM thrombin in vitro (*15*), suggesting that GpIb-IX-V alone is not sufficient to aggregate platelets.

The differing interpretations are not mutually exclusive, and their breadth foreshadows the directions that future experiments are likely to explore. For example, both structures suggest that GpIbα might bind simultaneously to one thrombin through exosite II and to von Willebrand factor. Because the Celikel structure contains both thrombin-GpIb and unique thrombin-thrombin contacts, it suggests that thrombin binding may be cooperative. Both structures invoke thrombin bivalency to explain platelet signaling or aggregation, and these responses might not be elicited by engineered monovalent thrombins. Finally, both structures show unique contacts that should be evaluated further by mutagenesis. Such functional studies will be critical to determine which of the observed thrombin-GpIbα interfaces are biologically important.

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NEUROSCIENCE

Predicting Future Rewards

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Goal-directed behavior affects all areas of society, not just biology or medicine, as evidenced by two recent Nobel prizes for economics that were awarded for work on game theory. Game theory shows how people make decisions about what to purchase and when and the rationale for seeking goals or rewards (*1, 2*). The formalism of game theory is being used to analyze and interpret the neurobiology of motivated behavior (*3*). In their report on page 229 of this issue, Matsumoto *et al*. (*4*) investigate the regions of monkey brain that are activated during goal-directed behavior.

Our sense of which behavior to choose to reach a goal or obtain a reward is based on the perceived value of the reward, the effort needed to obtain it, and our previous experience about the likelihood of success. Information for anticipating reward is often provided through associations of these factors with environmental cues. Research over the past decade has yielded a great deal of information about how and where assessments related to anticipated reward occur in the brain.

Reward-seeking behavior includes two steps. One is to predict what the outcome of behavior will be; the other is to evaluate whether the predictions are met, that is, to construct an error signal (*5*). Schultz and colleagues (*6*) recognized that the dopamine neurons of the substantia nigra and ventral tegmental area carry a signal

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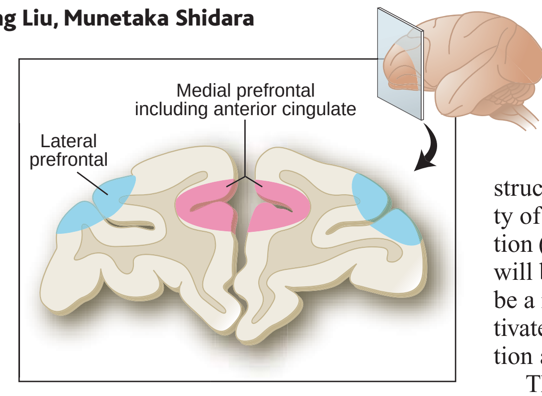

The lateral and medial prefrontal cortex areas of monkey brain.

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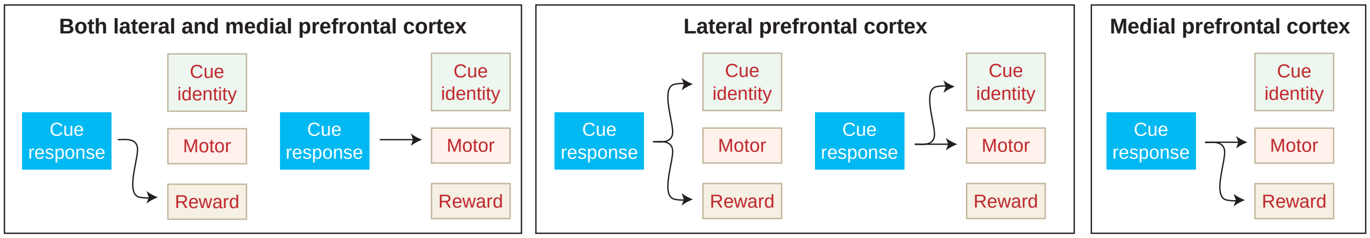
that appears to encode prediction error. How the brain makes predictions is a complex process that is not yet clearly understood. However, it appears that many brain regions participate. For example, the ventral striatum, medial temporal lobe areas, and parietal areas all have signals related to reward expectation or prediction (*3, 7, 8*).

Judging the relative values of stimuli for making choices about which action to take to obtain a reward seems to depend critically on the prefrontal regions (areas rich in dopamine) of the brain's frontal lobes (see the first figure). The prefrontal regions are important for keeping track of the present and predicting the future (*9*). In their report, Matsumoto *et al*. compare different groups of neurons in the lateral and medial frontal lobes of monkey brain for their ability to predict a juice reward (*10*).

The lateral prefrontal cortex seems to be important for working memory, the type of memory that has constant rehearsal such as remembering a phone number for a short time or remembering where one is in a sequence of actions or tasks. Neurons in this brain area often start responding when a cue to the behavior needed to obtain a reward appears. The activity continues until the onset or end of the correct motor action, even if the movement is delayed for several seconds. This "delay" activity seems related to working memory in that it extends through the delay between the instruction and the reward (*10*). The intensity of this activity is modulated by information (from the cue) about how much reward will be delivered (*11*) or whether there will be a reward (*12, 13*). Thus, a visual cue activates a persistent signal giving information about reward expectation.

The medial prefrontal cortex, particularly the anterior cingulate cortex, is likely to be important in judging a reward's value. Humans with severe lesions of the anterior cingulate cortex have a blunted emotional affect to pain and other emotionally charged events, essentially appearing apathetic. A recent behavioral study in monkeys showed that the anterior cingulate cortex is important for assessing the value of an action for obtaining a predicted outcome (*14*). Both functional imaging in humans and recording from single neurons in monkeys have shown that medial prefrontal areas including the cingulate cortex are activated during periods of expectancy about the imminence and probability of a reward (*15–18*), when there is seemingly a strong emotional component to the state of expectancy.

To compare these lateral and medial prefrontal regions directly, Matsumoto and colleagues recorded from neurons in the lateral and medial prefrontal areas of monkey brain during a single behavior: a "go-nogo" task. Their monkeys learned to carry out one of two motor "responses"—pull a lever (go) or do not move (nogo)—upon seeing one of two pictures. After the correct action, a tone indicated that the correct ac-



Seeking rewards. Matsumoto *et al.* (*4*) describe neuronal responses elicited by a visual instructing cue in the lateral and medial prefrontal regions of monkey brain. Four major categories of information were provided in the responses. In both lateral and medial prefrontal cortex, some neurons predicted whether the reward would be given (arrow), and the responses did not encode information about the cue's identity or the correct action. Another group of neurons predicted which action would be taken, regardless of which cue had appeared or whether there would be a reward. In the lateral prefrontal cortex only, some neurons responded to one particular cue and predicted whether there would be a reward, regardless of the motor action. Another group of neurons responded to one particular cue and predicted which action would be taken, regardless of whether there would be a reward. In the medial prefrontal cortex only, neurons predicted a particular action and whether there would be a reward.

tion had been performed. A juice reward was given for only one of the two correct actions. An important feature was that after extensive training the monkeys recognized changes in the stimulus-action-reward linkage quickly and easily so that all combinations could be used. Neurons in both areas exhibited responses that were triggered by the cue's appearance. The authors found that in both lateral and medial areas, some of these cue-elicited responses predicted the reward contingency (see the second figure) but were independent of both the stimulus identity and the particular action taken (go or nogo) (figure 3E of the Matsumoto *et al.* report, reward only, R). Both brain regions also contained cue-elicited responses predicting one movement regardless of the stimulus or reward (motor, M). However, in the lateral prefrontal cortex only, some cue-elicited responses predicted one cue and one movement (visual-motor, VM) or one cue and one reward (visual-reward, VR). In the medial prefrontal cortex only, some cue-elicited responses predicted one action and one reward (motor-reward, MR).

The lateral prefrontal cortex seems to hold information provided by the cue about the reward and its value, whereas the medial prefrontal cortex interprets cues to provide information for anticipating the act or condition needed for the current reward contingency to be fulfilled. Thus, these results support the view that the prefrontal cortex is important for predicting a reward and planning to obtain it. The next step will be to learn how the interactions of these prefrontal areas with each other and with other brain areas lead to the prediction of reward and its value for motivating future action.

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ANTHROPOLOGY

New Guinea: A Cradle of Agriculture

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Since the 1930s, botanists and archaeologists have suggested that plant domestication developed independently in a few core areas and spread from there across the world. With its diversity of root and tuber plants, spices, fruit trees, and other crops, Southeast Asia seemed to be a perfect candidate for such a core area (*1*–*3*). Some authors included New Guinea in their scenarios, but generally the island was seen as a passive recipient of domesticated plants and animals from the Southeast Asian heartland.

Today, the picture has changed completely. From a "Neolithic backwater," New Guinea has turned into one of the few pristine centers of early plant domestication (see the first figure). There is increasing evidence that two of the world's most valuable crops, sugar cane and banana, originated there. On page 189 of this issue, Denham *et al.* (*4*) provide convincing evidence that the banana was cultivated in New Guinea as long as 7000 years ago.

Archaeological and paleoenvironmental studies have long hinted at the antiquity of New Guinean plant cultivation (*5*), but direct evidence was tenuous. Similar to other humid tropical areas, larger plant remains, such as seeds and fruits, do not preserve well in the swampy soils of the New Guinean highlands where agriculture was proposed to have emerged. Sediment and pollen data provided evidence for deforestation and erosion since at least 7000 years ago (*6*). It remained unclear, however, whether early farmers had cleared the montane forest for their fields, or hunter-gatherers had burned the forest to improve access to wild plants and animals.

One of the best-studied archaeological sites in the New Guinean highlands is Kuk in the Wahgi Valley. There, Golson and his team discovered a series of buried, meter-deep channels, which they interpreted as drainage canals dug by early root-crop cultivators as early as 9000 years ago (*7*). However, the exact nature of the channels and the interpretation of their function remained controversial (*8*, *9*).

Denham *et al.* (*4*) now report new insights into the development of plant exploitation and land-use practices at Kuk. Well-dated archaeological features such as pits, stake holes, mounds, and ditches show

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